Attenuated PTH Responsiveness to Vitamin D Deficiency among Patients with Type 2 Diabetes and Chronic Hyperglycemia

Ahmed F. Al-Jebawi [a], Ahmed H YoussefAgha [b], Hanan Sulaiman Al Suwaidi [c], Moza Saif Albadwawi [c], Asma Shabib Al Marzooqi [c], Ashjan Hassan Banihammad [c], Samia Hussain Almarzooqi [c], Mouza Khalifa Alkaabi [c].

a-Indiana University School of Medicine, Indianapolis, Indiana, USA.
b-Indiana University School of Public Health, Bloomington, Indiana, USA
c-Dubai Diabetes Center, Dubai Health Authority, Dubai, United Arab Emirates

ABSTRACT

Background

The short and long-term relationship between hyperglycemia and PTH level among patients suffering from both diabetes type 2 and vitamin D deficiency were evaluated.

Methods

This was a cross sectional study performed at Dubai Diabetes Center, UAE. To demonstrate the relationship between hyperglycemia and PTH level, subjects with type 2 diabetes and vitamin D deficiency (124 adults) were divided into 4 groups based on their FPG and HbA1c levels.

Results

Mean vitamin D and PTH levels among subjects with HbA1c≤7% (53 mmol/mol) were 14.05 ng/ml and 19.51pg/ml respectively. On the other hand, mean vitamin D and PTH levels among subjects with HbA1c≥10% (86 mmol/mol) were significantly lower at 11.77 ng/ml and 17.75pg/ml respectively. The product of vitamin D and PTH among subjects with an HbA1c≤7% (53 mmol/mol) was 250.380, compared with only 197.710 among subjects with HbA1c≥10 (86 mmol/mol). Regression analysis for subjects older than 50 years shows a significant negative effect of HbA1c on the PTH level. Mean calcium level among subjects with HbA1c≤7% (53 mmol/mol) was 8.80 mg/dl compared with 8.94 mg/dl when HbA1c is ≥10% (86 mmol/mol) with no statistical difference. Although high FPG was associated with a lower PTH level, such association was not statistically significant.

Conclusions

Chronic hyperglycemia, as assessed by A1C level, is associated with a significantly attenuated PTH responsiveness to vitamin D deficiency without a significant change in calcium level. On the other hand, there was no significant association between FPG and PTH level.

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Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; BUN, blood urea nitrogen; cCa, corrected calcium; FPG, fasting plasma glucose; HbA1c, glycosylated Hemoglobin Type A1C; Mg, magnesium; PTH, parathyroid hormone; PO4, serum Phosphorus; RUCa, random urine calcium to creatinine ratio; sCa, measured serum calcium; 25(OH) Vitamin D, 25 Hydroxy-Vitamin D; UAE, United Arab Emirates.

1. Introduction

Vitamin D deficiency and diabetes represent two of the most common metabolic health problems in the United States and the whole world. It is estimated that 387 million people had diabetes in 2014 and that by 2030 this may rise well above half a billion cases (1). The number of adults with diagnosed diabetes in the United States nearly quadrupled, from 5.5 million to 21.3 million during the period from 1980 through 2012 (2). Among adults, about 1.7 million new cases of diabetes are diagnosed each year. If this trend continues, as many as 1 out of every 3 adults in the United States could have diabetes by 2050 (2). Meanwhile, several reviews have found a global prevalence of vitamin D deficiency. In 2008, it was estimated that one billion individuals have vitamin D deficiency (25OH Vitamin D <20 ng/ml) (3). Despite the adequate UVB radiation in low latitude geographic locations, vitamin D deficiency was still found to be a very common health issue (4). Similarly, the prevalence of vitamin D deficiency is still quite high in industrialized countries despite the implementation of vitamin D fortification programs for many years (5-8). Although the association between diabetes and vitamin D deficiency has been proved (9), it is still unclear whether it is a cause and effect relationship or if vitamin D deficiency is merely a consequence of obesity. Since hypovitaminosis D causes a compensatory increase in the secretion of PTH; calcium levels usually remain within the normal limits. PTH restores eucalcemia through its effects on the kidney and bone. At the kidney level, PTH increases the conversion of calcidiol to calcitriol by 1alpha-hydroxylase. Furthermore, PTH increases the renal distal tubule reabsorption of calcium, and excretion of phosphorus. The bone effect of PTH is mediated through the PTH direct stimulatory effect of the osteoclasts and the indirect effects of calcitriol in enhancing further osteoclast activation and bone resorption (10). In addition to its effects on the kidney and bone, the increased levels of calcitriol stimulate the active intestinal absorption of calcium and phosphorus (10). Several factors have been demonstrated to modify the serum PTH response to low circulating 25(OH) vitamin D. Magnesium deficiency was found to play an important role in functional hypoparathyroidism (11). In men with vitamin D deficiency, it was demonstrated that higher levels of IGF1 and testosterone are associated with a lower PTH level whilst greater BMI is linked to a higher PTH level. On the other hand, for women suffering from vitamin D deficiency, the combined effect of smoking, BMI and cystatin C appears to explain 36.2% of the variability in the PTH level. Smoking has the greatest association with reduced PTH levels, explaining 20.8% of the variability in the PTH level (12). Circadian variations in PTH, (13) and the variations in Vitamin D binding protein (14) and its impact on the free Vitamin D levels are some other examples of these factors.

Although the effect of endocrinopathy on hyperglycemia was evaluated extensively, there is little data on the effect of hyperglycemia on the function of the endocrine system. Since vitamin D deficiency is very common among patients with diabetes, the relationship between hyperglycemia and the PTH level may answer many questions related to calcium and bone metabolism. If hyperglycemia will enhance PTH production, the higher levels of PTH may increase bone turnover (15) and possibly increase fracture risk (16, 17). On the other hand, if hyperglycemia will reduce the PTH levels, it may result in clinically significant hypocalcemia. The main objective of this study is to evaluate the relationship between hyperglycemia and the parathyroid hormone level among patients suffering from vitamin D deficiency and type 2 diabetes.

2. Methods

This is a cross sectional study consisting of 124 consecutive patients. All subjects are adults with type 2 diabetes mellitus and vitamin D deficiency (defined as 25(OH) vitamin D level of less than 30 ng/ml) who came to Dubai Diabetes Center for the management of their diabetes during the period between February1st to April30th, 2012. All participants were United Arab Emirates citizens who live in the Emirate of Dubai (latitude 25 N). The exclusion criteria were tobacco smoking, alcohol intake, renal impairment (eGFR<70 mL/min/1.73 m^2), abnormal urinary albumin excretion (urine albumin/ creatinine ratio >30 mg/g), pregnancy and the use of any drugs which can influence bone metabolism such as thyroid hormones, steroids, products containing vitamin D or its derivatives, calcium, magnesium, lithium, anti-convulsants, sex hormones and medications used for the treatment of osteoporosis. All enrolled patients met with a registered dietician and were put on a nutritional plan according to the American Diabetes Association nutrition guidelines (18). A daily intake of 1,000–1,500 mg of calcium was recommended.

Body weight and height were measured with the subject barefoot and wearing light clothing and used to calculate the body mass index (BMI). All participants were required to fast for at least 8 h before having the following lab tests: HbA1c (%), serum creatinine (mg/dl), BUN(mg/dl), serum calcium (mg/dl), albumin (g/dl), serum phosphate (mg/dl), alkaline phosphatase ALP (IU/L), magnesium (mmol/L), total (both 25(OH)D2 and 25(OH)D3 25 hydroxyvitamin D) (ng/ml), intact PTH (pg/ml) and urine calcium and creatinine. Calcium was corrected to albumin level by using the following formula: serum calcium+0.8 (4-serum albumin). Venous blood sampling was performed using a tourniquet to help locate and define peripheral veins to achieve successful and safe venipuncture. As prolonged venous stasis may affect the accuracy of calcium level measurement, the application of a tourniquet did not exceed one minute.
The HbA1c determination was based on the turbidimetric inhibition immunoassay (TINIA) for hemolyzed whole blood. Quality control procedure was performed according to HITACHI 912 Analyzer Calibration Procedure PD-RBIO-HT-002. Albumin, Magnesium, Phosphorus (Phosphate-PO4) and Alkaline Phosphatase measurement was made on Hitachi 912 analyzer by Colorimetric assay with endpoint method. External Quality Control is carried out every two weeks through Bio-Rad Clinical Chemistry Control. Serum calcium was assayed by a method

according to Schwarzenbach with o-cresolphthalein complexone. Intact PTH (Parathyroid Hormone) determination was measured by using RIA technique on the Gamma Counter Wizard 1470. The Intact PTH present in the standards, controls or the samples is first incubated with the incubation buffer for 60 minutes with continuous shaking. This will allow the PTH to be captured to the anti- PTH coating the tube. After washing with the wash buffer, the iodine 125 labeled anti- PTH antibodies are added. Another 60-minute incubation with continuous shaking. Washing with the wash buffer is then performed. The radioactivity bound to the tube is proportional to the concentration of PTH present in the standards, controls and sample. The kit was obtained from Bioosource. Internal quality control is assayed with every run and external quality control is performed every two weeks by Bio- Rad Set 2 assayed hormone control. 25(OH) Vitamin D total determination was based on using RIA technique on the Gamma Counter Wizard 1470. A fixed amount of 125I labeled 25OH vitamin D competes with the 25OH vitamin D2 and 25OH vitamin D3 from treated samples for affixed amount of a specific monoclonal antibody site immobilized to inner surface of tubes. After 2 hours of incubation, aspiration steps terminate reaction. The tube washed twice and read on gamma counter. The kit is from Diaosource. Internal quality control is assayed with every run and external quality control is performed every two weeks by Bio- Rad. The RIA method intra assay %CV coefficient of variation is 4.8%.

2.1 Statistical Analysis

This study included (n=124) diabetic patients through a convenience (non-probability) sampling method from one of the largest diabetes centers in the city of Dubai, United Arab Emirates. After records with missing data (14%), and/or univariate outliers (3%) were excluded, the sample size became (106). No multivariate outliers were detected. Results of evaluation of assumptions of normality, multicollinearity and homogeneity of variance were satisfactory on the target variables (HbA1c, FPG, PTH, 25(OH) vitamin D, cCa, and Mg). After the subjects with missing data and outliers were excluded, the sample size was still greater than what was required for regression test criteria (106)>50+8*(5 IVs) for five independent variables (19). To demonstrate the relationship between chronic hyperglycemia and the PTH level, subjects were divided into 4 groups based on their HbA1c levels. HbA1c≤ 7.0% (53 mmol/mol) (n=36) was considered as a good control, HbA1c 7.1-8.4% (54-68 mmol/mol) (n=42) as an inadequate control, HbA1c 8.5-9.9% (69-85 mmol/mol) (n=14) as a poor control and HbA1c≥10% (86 mmol/mol) (n=14) as a very poor control. On the other hand, to demonstrate the relationship between FPG and the PTH level, subjects were divided into 4 groups based on their FPG levels. FPG ≤130 mg/dl (n=37) was considered as a good control, FPG 131-170 mg/dl (n=38) as inadequate control, FPG 171-200 mg/dl (n=11) as a poor control and FPG >200 mg/dl (n=19) as a very poor control. Number of subjects older than 50 years of age was 58 (27 males, and 31 females) while the number of those ≤50 years old was 48 (20 males, and 28 females). The PTH level was specifically compared between subjects who were older than 50 years of age with their younger counterparts.

Means trend analysis, simple linear regression, and a generalized linear model were used to answer the question whether HbA1c level affects the PTH response to vitamin D deficiency. On the other hand, generalized estimated equation (GEE) was used to answer the question whether magnesium level plays any role in the PTH response to vitamin D deficiency. Although GEE statistical method requires a large number of clusters to produce consistent estimates, we do believe we have fulfilled this requirement with our sample size and the fact that missing values are less than 5%. The GEE model in this study was built by using the following criteria: [1] the repeated subject is the patient-ID number; [2] the sample size is 106 cluster "patients". This number was found to be sufficient to study 5-12 exploratory variables (19). The sample size (106) was enough to run a regression model with a power percentage of 80%, alpha=0.05 and beta=0.20. Clusters with missing values were 14; [3] since the dependent variable (PTH) satisfied normality, the identity linked function was used; [4] the 25(OH) vitamin D (coded as VitD) and the HbA1c were the independent variables [5] the correlation structure "Exchangeable" was used.

Means trend analysis, simple linear regression, and a generalized linear model were used to answer the question whether HbA1c level is associated with a different response of the PTH to vitamin D deficiency. A generalized estimated equation (GEE) was used to answer three research points (1) whether magnesium level plays any role in the PTH response to vitamin D deficiency; (2) whether PTH is influenced by the product (interaction) of HbA1c and vitamin D *(HbA1c*VitD)* and (3) whether the regression relationship between PTH and both of HbA1c and vitamin D is different among patients who are older than 50 years of age compared with those of a younger age.

2.2 Ethical approval

Medical Research Committee of Dubai Health Authority had approved the study and an informed consent was obtained from all patients.

3. Results

3.1 Patients

In total, 47 male and 59 female adults were studied. The median age of all enrolled subjects was 55 years with a range between 34.8 and 76.2 years. Subjects' characteristics are shown in Table (1).

3.2 PTH response to vitamin D deficiency at different HbA1c levels

Figure (1) shows the mean levels of 25(OH) vitamin D, PTH, cCa, Mg and PO4 among the four HbA1c and FPG groups. There was a significant (P=0.028) inverse correlation between 25(OH) vitamin D level and HbA1c in both genders. Although 25(OH) vitamin D was also inversely correlated with the fasting plasma glucose (FPG), the inverse correlation between HbA1c and 25(OH) vitamin D was much stronger. The relationship between parathyroid hormone and 25(OH) vitamin D with each HbA1c group shown in Figure 2 is significant. The moderate correlation value was 0.56 for subjects with an HbA1c of ≤ 7 (53 mmo/mol), 0.2 for subjects with an HbA1c of 7.1-8.4 (54-68 mmol/mol), 0.46 for subjects with an HbA1c of 8.5-9.9% (69-

85 mmol/mol) and 0.53 for subjects with an HbA1c of ≥10 (86 mmol/mol) (P<0.005). Serum 25(OH) vitamin D concentrations ranged between 4.0-21.30 ng/ml (laboratory reference values: 30-100 ng/dl) with a mean value being 13.35 ng/ml. On the other hand, plasma levels of intact PTH ranged from 5.0-40.0 pg/ml (laboratory reference values: 6.2- 29.0 pg/ml) with a mean value being 17.67 pg/ml. Although PTH levels continued to increase with lower levels of 25(OH) vitamin D, our data showed that for the same level of 25(OH) vitamin D, PTH response is attenuated among patients with higher HbA1c levels. The data summarized in Figure (2) shows that hyperglycemia with higher HbA1c levels among patients with diabetes type 2 is associated with an attenuated PTH responsiveness to vitamin D deficiency. Although higher PTH levels are associated with lower levels of 25(OH) vitamin D, the negative slope becomes less steep when HbA1c is higher. In contrast, regression analysis did not show a significant association between FPG and the responsiveness of PTH to vitamin D deficiency.

Our results show that there is a significant association between PTH level and the interaction (the product) of HbA1c and 25(OH) vitamin D with a negative coefficient value of (*-0.064*, p<0.002). While the interaction (product) value of 25(OH) vitamin D and PTH among subjects with HbA1c≤7% (53 mmo/mol) was 250.380, it was only 197.710 among subjects with HbA1c≥10 (86 mmol/mol) (*-0.064*, p<0.002).

3.3 Vitamin D and HbA1c levels may predict PTH level

The GEE analysis provided the following findings:
(1) Although the mean trend analysis (Fig 1) shows that a higher HbA1c is associated with a lower Mg level, the change in Mg level was not statistically significant.
(2) PTH was shown to be predicted from the HbA1c interaction with vitamin D, the following model predicts PTH level for all subjects:

$$PTH = 24.341 - 0.064\ HbA1c(\%) * VitD,\ p<0.002.$$

(3) Age is an important factor to predict the PTH level. The following model is able to more accurately predict the PTH level for subjects who are older than 50 years of age:

$$PTH = 34.153 - 0.680\ VitD - 2.523\ HbA1c\ (\%),\ p<0.003.$$

This relationship clearly shows the negative effects of both HbA1c and (25) OH vitamin D on the dependent variable PTH with negative slopes of (-0.68) and (-2.523) respectively. This obvious relationship was not seen among subjects who are younger than 50 years.

4. Discussion

In this cross sectional study, we showed that chronic hyperglycemia is associated with a lower parathyroid hormone level among patients with vitamin D deficiency and type 2 diabetes. Few studies have been conducted to examine the relationship between hyperglycemia and the parathyroid hormone (PTH) secretion. Nguyen et al showed that hyperglycemia due to glucose load induced an increase in calcium excretion among healthy subjects following oral glucose tolerance test (OGTT) with 75g carbohydrate (20). Venkataraman et al showed that serum calcium, Magnesium and phosphorus values declined significantly in normal neonates after an oral glucose load, and the decline in serum calcium was significantly correlated with the amount of glucose ingested. They showed that the above changes were associated with a significant

compensatory rise in serum PTH but no significant change in the ionized calcium level (21). On the other hand, other studies have demonstrated a suppressive effect of acute hyperglycemia on the parathyroid hormone production with a decline in serum calcium and an increase in urinary calcium excretion (22).

Secondary hyperparathyroidism is a well-known consequence of low 25(OH) vitamin D level. Since blunted PTH level was not thoroughly evaluated, only few factors were found to attenuate the responsiveness of PTH to low vitamin D levels. Due to the fact that low magnesium levels may attenuate the PTH secretion, magnesium level was specifically evaluated in our available data. Although it was slightly lower (mean=1.84) among patients with higher HbA1c levels (>7.0), the difference in the magnesium level was not statistically significant. In our study, we could simply replicate the well-known hyperbolic inverse association between 25(OH) vitamin D and PTH levels for all HbA1c and FPG levels through curve estimation regression analysis (Fig. 2). Since there is still little literature on the relationship between 25(OH) vitamin D and glycemic control, we studied this correlation among all enrolled patients. Our data is clearly showing that chronic hyperglycemia is associated with a lower parathyroid hormone level among patients with type 2 diabetes and vitamin D deficiency. In fact, the results among the groups that have the largest number of subjects (the groups of A1c of less than 7 and 7.1-8.4) show more obvious difference in the slope (i.e. the slope becomes much less steep when HbA1c is higher). Furthermore, the difference in the PTH mean and R2 value between these two groups is more pronounced than any other groups (PTH mean dropped from 19.51 among the group of HbA1c of less than 7 to 16.03 among the group of HbA1c of 7.1-8.4) and the R2 value dropped from 0.32 among the group of HbA1c of less than 7 to 0.04 among the group of HbA1c of 7.1-8.4). Therefore, the results among subjects of these two groups show much larger differences than any other groups. The slope value of the 7.1-8.4 group is out of the expected trend range probably because the variance is high and homoscedastic in this group. This is most likely due to the fact that the HbA1c was falling in the middle between the good and poor control. For the sake of simplicity, the only dependent variable that was included in this simple regression model was vitamin D level. The influence of other factors such as age, gender, duration of diabetes was not included.

Since there is little literature on the association between hyperglycemia and the PTH level, the study was designed to evaluate the relationship between both FPG and HbA1c and the PTH level among patients with vitamin D deficiency and type 2diabetes. In our study, we showed that higher HbA1c levels are associated with an attenuated PTH responsiveness to vitamin D deficiency. Although high FPG was associated with a reduced PTH levels, the results were not statistically significant. Interestingly, the groups of A1c of less than 7 and 7.1-8.4 have at least one subject with the 25-hydroxyvitamin D of about 5 ng/ml with the most robust PTH response. Despite the fact that the duration of diabetes and degree of hyperglycemia have consistently been identified as predictors of microvascular complications, multiple studies have shown that many patients with diabetes may escape complications. The Medalist Study is one of these example studies that suggest the presence of certain protective factors against developing the complications. This assumption was based on the data of individuals with extreme duration of type 1 diabetes who are either protected from or have markedly slower progression of diabetic retinopathy (23). The significant number of complication free diabetic patients may strongly

indicate that there are protective molecular, physiologic or genetic mechanisms that protect against the toxic effects of hyperglycemia. Figure 2 clearly shows that there are still some subjects with a very good PTH responsiveness to vitamin D deficiency despite the high HbA1c level. Nevertheless, the magnitude of the highest two PTH levels among each of the four HbA1c groups was still decreasing with the increasing levels of HbA1c. Furthermore, like any other complications of diabetes, there are other potential risk factors that may play an important role in the pathogenesis of "attenuated PTH responsiveness to hypovitaminosis D" among patients with type 2 diabetes. Such factors may include duration of diabetes, hypertension, hyperlipidemia, genetic risk factors and the presence of certain inflammatory bio-markers. Since our study did not evaluate the impact of any of these potential risk factors on the PTH responsiveness, the data in figure 2 is only representing a simple regression model (i.e. only one dependent variable "vitamin D level" was included) for simplicity. Because there was no association between the demographics of BMI and gender and the PTH level, it was concluded that the selection criteria had achieved homogeneity among all subjects and therefore, demographic adjustment was excluded from these models. Interestingly, corrected calcium level did not significantly change despite the fact that the higher HbA1c level was associated with a significant decrease in the PTH level among patients with vitamin D deficiency. Moreover, neither the phosphate nor the urine calcium (urine calcium/urine creatinine ratio) showed a significant change among the four groups of HbA1c. Interestingly, the chronic hyperglycemia-associated attenuation of PTH secretion was only seen among subjects (males and females) who are older than 50 years of age. Since we do not have a clear explanation for this association, we believe that the most likely reason is the fact that older people are more likely to have their diabetes for a longer period of time with a longer exposure to chronic hyperglycemia.

Nevertheless, few in vitro studies have shown a direct suppressive effect of high concentration of glucose on PTH secretion from cultured bovine parathyroid cells (24). Although it was shown that an oral glucose load induced hyperglycemia promotes a significant decline in serum PTH in postmenopausal women (25), to our knowledge, no data are available showing the relationship between chronic hyperglycemia and PTH or calcium levels among patients suffering from type 2 diabetes. Since hyperglycemia is usually associated with higher levels of insulin and other endocrine changes, such as abnormalities of gonadal and hypophyseal axis, the exact pathophysiological effects of hyperglycemia on the PTH production and bone metabolism remain complex and would need more investigations. The reduction in bone resorption after intravenous administration of insulin (26) is just an example of these biochemical bone changes that may occur after developing hyperglycemia. Surprisingly, calcium levels did not change significantly among subjects with a higher HbA1c despite the fact that their PTH level was significantly lower. This finding is consistent with many other observational studies that have shown a normal calcium level among patients suffering from diabetes and vitamin D deficiency (27). Although it was initially thought that diabetic patients may have a primary disturbance of bone metabolism with a negative net calcium balance (28), Ishida et al. reported that type 2 diabetics exhibited higher serum parathyroid hormone related peptide (PTHrP) levels than control subjects (29). They proposed that elevated PTHrP levels might play a compensatory role in calcium homeostasis in diabetic patients. Additional evidence was further obtained by the

group of Suzuki et al. (30) who found a significant positive correlation between calcemia and PTHrP in type 2 diabetic patients. They speculated, therefore, that the increased levels of serum PTHrP in type 2 diabetic patients could compensate for the decreased PTH levels. Because their data had shown a positive correlation of PTHrP with glucose levels, they concluded that PTHrP is related to the presence of type 2 diabetes and not to the patient's obesity and hormonal status. Obviously, our data does not include the PTHrP level to allow us draw any conclusion on the role of PTHrP level among subjects with higher HbA1c, low vitamin D and attenuated PTH levels who still have a normal calcium level. However, the possibility of higher PTHrP level among these patients cannot be excluded especially with the fact that the urinary calcium or serum phosphorus levels among the different HbA1c groups are not significantly different. Since PTHrP has a similar effect to the PTH on the distal renal tubules, the possibility that higher levels of PTHrP are stimulating the reabsorption of calcium in the distal renal tubules through binding to the PTH receptors needs to be further evaluated.

To the best of our knowledge, this is the only study that has evaluated the relationship between hyperglycemia and PTH responsiveness to vitamin D deficiency. Nevertheless, the current study had a few limitations. First, this was a cross-sectional study, and we recommend long-term prospective studies to evaluate any possible cause-and-effect relationships. Second, obtaining a larger sample size would be more representative of the population. Third, we did not include people of different ethnic backgrounds to determine whether the risk and degree of these complications vary according to ethnicity. Fourth, we did not include the duration of diabetes and the medications used for its treatment in our data. Fifth, PTHrP level was not measured among enrolled subjects.

5. Conclusion

Our findings indicate that chronic hyperglycemia is associated with a significantly attenuated PTH responsiveness to vitamin D deficiency without causing hypocalcemia. On the other hand, FPG is not associated with a significant decrease in PTH level. Interestingly, the chronic hyperglycemia-associated attenuation of PTH secretion was only seen among subjects (males and females) who are older than 50 years of age.

Due to the fact that potential bone effects of low PTH levels among patients with diabetes have not been elucidated thoroughly, further studies addressing the possible adverse (or beneficial) effects of low PTH with its altered calcium homeostasis are warranted.

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Conflicts of interest disclosures

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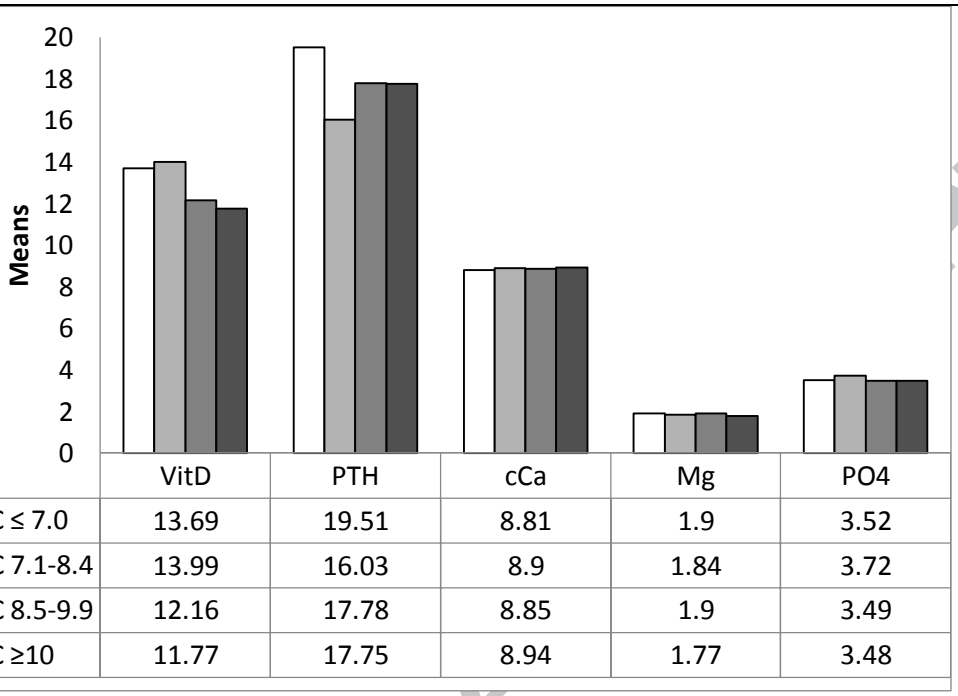
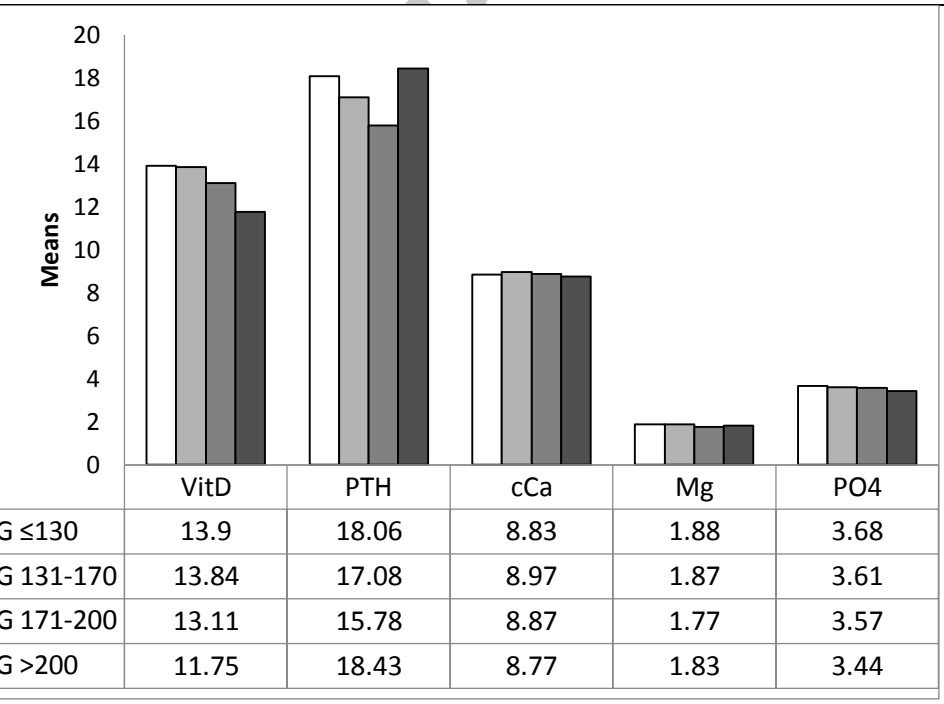
Fig 1: Means trend by HbA1c and FPG levels.



	VitD	PTH	cCa	Mg	PO4
A1C ≤ 7.0	13.69	19.51	8.81	1.9	3.52
A1C 7.1-8.4	13.99	16.03	8.9	1.84	3.72
A1C 8.5-9.9	12.16	17.78	8.85	1.9	3.49
A1C ≥10	11.77	17.75	8.94	1.77	3.48



	VitD	PTH	cCa	Mg	PO4
FPG ≤130	13.9	18.06	8.83	1.88	3.68
FPG 131-170	13.84	17.08	8.97	1.87	3.61
FPG 171-200	13.11	15.78	8.87	1.77	3.57
FPG >200	11.75	18.43	8.77	1.83	3.44

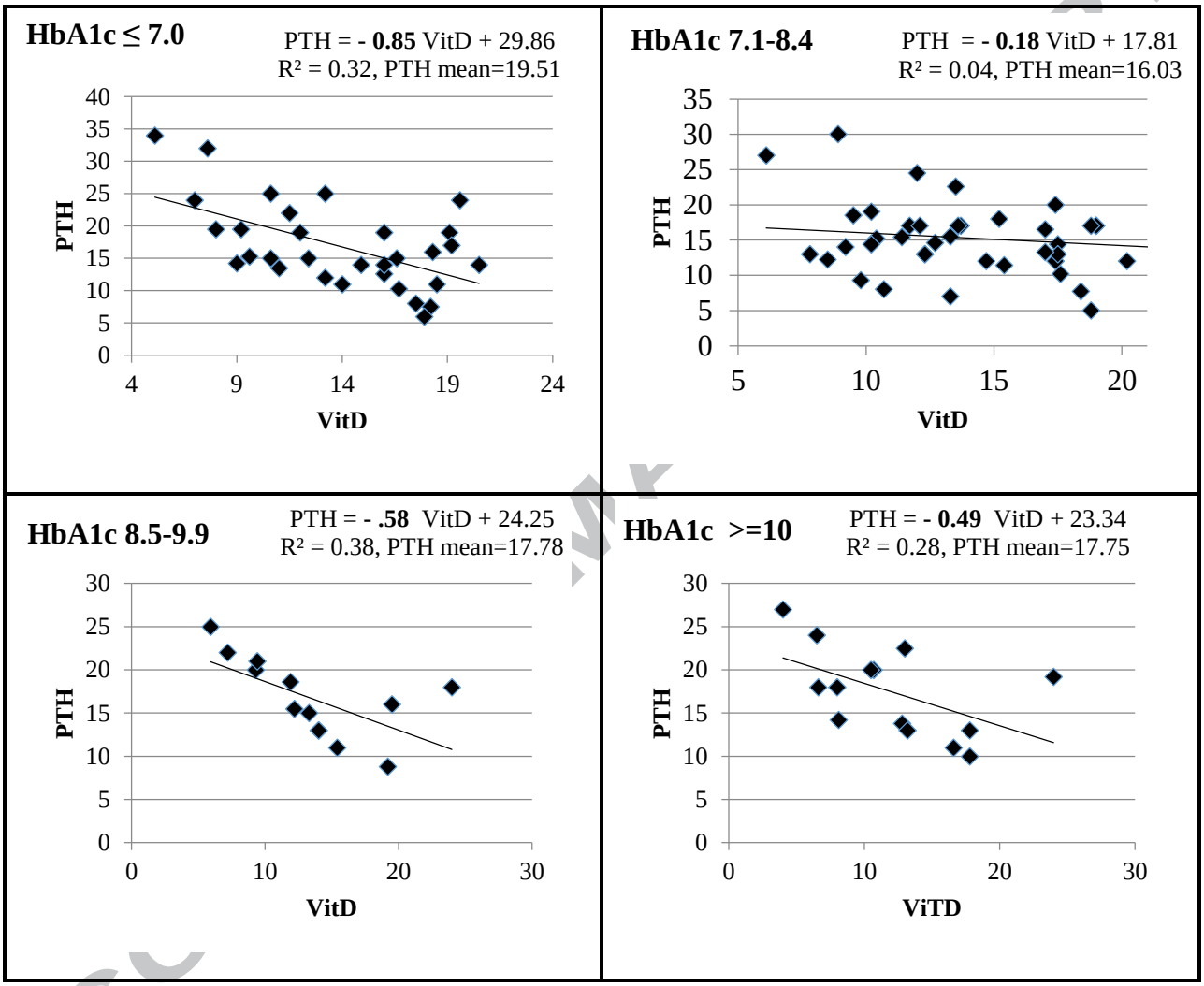
Abbreviations: A1c, glycosylated Hemoglobin Type A1c; VitD, 25 Hydroxy-Vitamin D.

Fig 2: PTH concentrations Regression on Vitamin D at different levels of HbA1c

Although the PTH level increases with lower levels of 25(OH) vitamin D, the negative slope becomes less steep when HbA1c is higher.

Slope value (-0.85)
with HbA1c ≤ 7% (53 mmo/mol)

Slope value (-0.18)
with HbA1c 7.1-8.4% (54-68 mmo/mol)



Slope value (-0.58)
with HbA1c 8.5-9.9% (69-85 mmo/mol)

Slope value (-0.49)
with HbA1c % ≥10% (86 mmol/mol)

Figure 3:

(PTH x Vitamin D) Product significantly decreases with higher HbA1c levels.

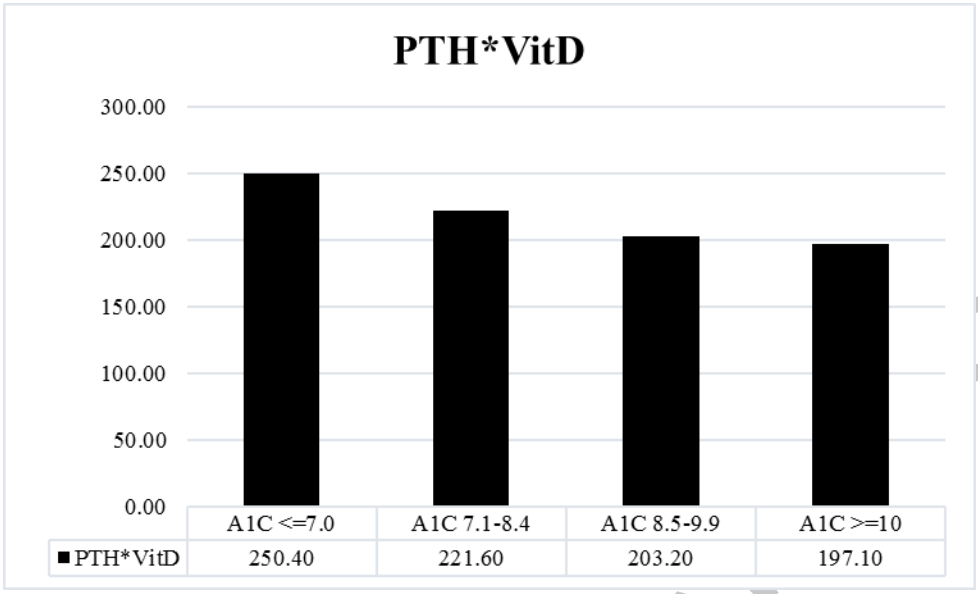


Table 1 Descriptive Statistics

	Male (n=46)				Female (n=60)			
Variable	**Mean**	**Std Dev**	**Lower 95% CL for Mean**	**Upper 95% CL for Mean**	**Mean**	**Std Dev**	**Lower 95% CL for Mean**	**Upper 95% CL for Mean**
Age (y)	54.98	10.86	51.63	58.32	51.32	12.2	48.14	54.5
Body weight (Kg)	104.9	11.47	101.4	108.3	105.6	13.12	102.2	109
Height (m)	1.67	0.08	1.65	1.69	1.57	0.07	1.55	1.58
BMI (kg/m2)	30.56	4.97	29.07	32.06	33.5	6.26	31.88	35.11
FPG (mg/dL)	153.1	49.04	138.5	167.6	156.8	52.71	143.2	170.4
Albumin (g/dL)	4.52	0.32	4.43	4.62	4.29	0.34	4.2	4.37
cCa (mg/dL)	8.8	0.41	8.68	8.92	8.93	0.42	8.82	9.04
sCa (mg/dL)	9.22	0.39	9.1	9.33	9.16	0.42	9.05	9.27
PO4, (mg/dL)	3.45	0.43	3.32	3.57	3.71	0.59	3.55	3.86
Mg (mg/dL)	1.92	0.18	1.86	1.97	1.82	0.19	1.77	1.86
ALP (IU/L)	65.59	16.95	60.55	70.62	75.2	22.5	69.39	81.01
BUN (mg/dL)	30.89	8.36	28.38	33.4	24.38	8.08	22.21	26.54
HbA1c (%)	7.7	1.91	7.13	8.27	7.99	1.47	7.61	8.37
Intact PTH (pg/mL)	16.29	6.69	14.3	18.28	18.73	7.62	16.76	20.7
25(OH) VitD (ng/mL)	14.88	4.12	13.66	16.11	12.18	3.98	11.15	13.2
RUCa mg/G creatinine	7.51	5.22	5.45	9.58	6.09	4.01	4.36	7.82

Highlights

Chronic hyperglycemia is associated with a significantly attenuated PTH responsiveness to vitamin D deficiency without causing hypocalcemia.

Acute hyperglycemia is not associated with a significant decrease in PTH levels among patients suffering from type 2 diabetes and vitamin D deficiency.